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A Phase 2 Trial of Intravesical Gemcitabine and Docetaxel in the Treatment of Bacillus Calmette-Guérin–Naïve Nonmuscle-Invasive Urothelial Carcinoma of the Bladder

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Full-length article available at https://doi.org/10.1097/JU.0000000000003977.

Study Need and Importance: For decades, the mainstay treatment for patients with high-risk nonmuscle-invasive bladder cancer (NMIBC) has been intravesical treatment with bacillus Calmette-Guérin (BCG). However, amidst widespread BCG shortages researchers have sought alternative treatment options that can be utilized in the BCG-naïve setting. Combination intravesical gemcitabine and docetaxel (GemDoce) has demonstrated efficacy as a second-line therapy for patients with BCG-unresponsive NMIBC. In this context, we performed a prospective single-arm open-label phase 2 trial for patients with BCG-naïve high-risk NMIBC. Intravesical GemDoce was administered weekly for 6 weeks as induction followed by monthly maintenance therapy for 2 years among responders. The primary end point was 3-month complete response rate, and secondary end points included adverse events (AEs) and 12-month complete response rate.

What We Found: Between August 2020 and August 2022 we enrolled 25 patients with median follow-up of 19.6 months. The pretreatment pathologic stages were high-grade (HG) T1 with carcinoma in situ (CIS; n = 7), HGT1 without CIS (n = 6), HGTa (n = 9), and CIS alone (n = 3). The 3-month and 12-month CR rates were 100% and 92%, respectively. Two patients with pretreatment HGT1 had HGT1 recurrences at 9 and 12 months. No patients progressed to T2 disease, underwent radical cystectomy, or had radiographic evidence of metastatic disease. Grade 1 AEs were common (23/25 patients) including hematuria, urinary frequency, urgency, and fatigue. Five patients (20%) experienced a Grade 3 AE including hematuria and UTI.

Limitations: This study was single center and single arm, and included a relatively low proportion of patients with CIS.

Interpretation for Patient Care: This single-arm phase 2 trial demonstrates that intravesical GemDoce was well tolerated with promising efficacy for patients with BCG-naïve high-risk NMIBC. These results provide impetus for conducting a prospective phase 3 trial comparing BCG and GemDoce (BRIDGE) in an analogous patient population.

https://doi.org/10.1097/JU.0000000000003977
Vol. 212, 95-103, July 2024
Printed in U.S.A.

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A Phase 2 Trial of Intravesical Gemcitabine and Docetaxel in the Treatment of Bacillus Calmette-Guérin–Naïve Nonmuscle-Invasive Urothelial Carcinoma of the Bladder

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Submitted December 23, 2023; accepted April 5, 2024; published April 23, 2024.

Funding/Support: Chad Holliday Research Fund.

Conflict of Interest Disclosures: The Authors have no conflicts of interest to disclose.

Ethics Statement: This study received Institutional Review Board approval (IRB No. J2020).

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Data analysis and interpretation: Kates, Patel, Gabrielson, Collins, Trock, Bivalacqua, Hahn.

Data acquisition: Kates, Patel, Chan, Schwartz, Singla.

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Editor's Note: This article is the third of 5 published in this issue for which Category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 250 and 251.

Purpose: Combination intravesical gemcitabine and docetaxel (GemDoce) has demonstrated efficacy as second-line therapy for patients with bacillus Calmette-Guérin (BCG)–unresponsive nonmuscle-invasive urothelial carcinoma of the bladder (NMIBC). In the context of widespread BCG shortages, we performed a phase 2 prospective trial to assess GemDoce for BCG-naïve NMIBC.

Materials and Methods: This study is a prospective, single-arm, open-label phase 2 trial for patients with BCG-naïve high-risk NMIBC. Intravesical GemDoce was given weekly for 6 weeks as induction followed by monthly maintenance therapy for 2 years among responders. The primary end point was 3-month complete response, and key secondary end points included adverse events (AEs) and 12-month recurrence-free survival.

Results: Twenty-five patients were enrolled between August 2020 and August 2022 with median follow-up of 19.6 months. The pretreatment pathologic stages were high-grade (HG) T1 with carcinoma in situ (CIS; n = 7), HGT1 without CIS (n = 6), HGTa (n = 9), and CIS alone (n = 3). The 3-month complete response rate was 100% and recurrence-free survival at 12 months was 92%. Two patients with pretreatment HGT1 had HGT1 recurrences at 9 and 12 months. No patients progressed to T2 disease, underwent radical cystectomy, or had any radiographic evidence of progressive disease. Grade 1 AEs were common (23/25 patients) including hematuria, urinary frequency, urgency, and fatigue. Five patients (20%) experienced a grade 3 AE including hematuria and UTI.

Conclusions: In this single-arm phase 2 trial, GemDoce was well tolerated with promising efficacy for patients with BCG-naïve high-risk NMIBC.

Key Words: bladder cancer, intravesical therapy, gemcitabine, docetaxel

Bladder cancer is the fourth most common solid malignancy in men in the US with an estimated 82,290 new cases being diagnosed in 2023.[1] Transurethral resection of bladder tumor (TURBT) followed by intravesical bacillus Calmette-Guérin (BCG) immunotherapy is the standard first-line treatment.[2] While up to 60% of patients have long term sustained remissions with intravesical BCG, 40% will ultimately experience tumor recurrence.[3-6] Additionally, the US and other countries experience frequent drug shortages of BCG due to manufacturing challenges, and these shortages have been shown to impact recurrence-free survival (RFS) for patients with

https://doi.org/10.1097/JU.0000000000003977
Vol. 212, 95-103, July 2024
Printed in U.S.A.

nonmuscle-invasive urothelial carcinoma of the bladder (NMIBC).[7] Finding alternatives to BCG for patients with newly diagnosed high-risk (HR) NMIBC thus constitutes an area of major unmet need.

Combination sequential intravesical gemcitabine and docetaxel (GemDoce) has shown promise in BCG-unresponsive HR NMIBC, with a multi-institutional retrospective series demonstrating a 12-month RFS of 60%.[7,8] Based on these promising retrospective data, GemDoce has been widely adopted by urologists and is a stated option in the National Comprehensive Cancer Network guidelines for patients with BCG-unresponsive HR NMIBC who desire an alternative to radical cystectomy.[9,10] More recently, GemDoce has been used for newly diagnosed BCG-naïve HR NMIBC, with a retrospective series of 107 patients reporting a 12-month RFS of 85%.[11] However, despite the widespread adoption of GemDoce for BCG-unresponsive NMIBC and initial promising reports in BCG-naïve NMIBC, there has not been a prospective clinical trial evaluating its efficacy and toxicity in bladder cancer. This lack of prospective data has made the existing GemDoce literature difficult to compare with other therapies or with BCG.

Given ongoing BCG shortages and promising retrospective data supporting use of GemDoce combination therapy, we conducted a prospective single-arm phase 2 clinical trial to evaluate intravesical GemDoce as a first-line therapy for patients with BCG-naïve HR NMIBC.

MATERIAL AND METHODS

Patient Selection

Patients with newly diagnosed high-grade (HG) NMIBC (HGTa, HGT1, or Tis stage) on TURBT obtained within 90 days of registration were included in the study. Patients with concurrent upper tract urothelial carcinoma or prostatic urethral carcinoma were excluded. Patients with any prior history of intravesical therapy with the exception of perioperative chemotherapy after TURBT were also excluded. All patients underwent a restaging TURBT by study investigators if they had HGT1 or incomplete resection at an outside hospital. Patient with resection at an outside hospital for carcinoma in situ (CIS) or HGTa had a second look cystoscopy by study investigators prior to enrollment.

The GemDoce treatment protocol was performed as has been previously reported.[11] One gram gemcitabine in 50 mL sterile water was slowly instilled into the bladder via a Foley catheter, and the catheter then was clamped for 60 minutes. The bladder was then drained and 37.5 mg docetaxel in 50 mL normal saline was then slowly instilled via the Foley catheter into the bladder. The catheter was again clamped for 60 minutes. Docetaxel was then drained and the catheter removed. Induction treatments were scheduled once a week for 6 weeks, and among patients exhibiting a posttreatment complete response (CR), maintenance GemDoce instillations were performed monthly for 2 years. At the end of the data lock, all patients completed and received all maintenance doses, so a total of 15 doses (6 induction, 9 maintenances to complete all 12 months).

Cystoscopic surveillance with urine cytology took place 12 weeks after initial GemDoce induction instillation, and every 3 months thereafter, including at 12 months. Patients with negative cystoscopy and positive cytology underwent complete endoscopic evaluations including all of the following: cystoscopy, blue light cystoscopy if available, bladder barbotage cytology, bilateral upper tract barbotage cytologies, bilateral retrograde pyelograms, random bladder biopsies, and prostatic urethral biopsies. Upper tract imaging, with CT urogram, was obtained on every patient either prior to or after NMIBC diagnosis.

Definition of End Points

The primary end point was 3-month CR rate, which was defined as the proportion of patients who demonstrated no evidence of recurrent HG urothelial carcinoma of the bladder of any stage at the 3-month posttreatment disease assessments. The secondary end points were 12-month RFS defined similarly, and the safety and toxicity of the therapy. A positive urine cytology was considered a recurrence for the purposes of these end points, although patients with a negative workup for an HG cytology were allowed to remain on GemDoce treatment.

Statistical Plan, Data Collection, and Analysis

This study comprised a single-center, single-arm, prospective phase 2 trial with a Simon's 2-stage design.[12] The null hypothesis was a 35% response rate vs a 1-sided alternative of 60%. In the first stage, 18 patients were accrued, followed by an interim analysis. If there were 6 or fewer responses in these 18 patients, the study would be stopped. Otherwise, 8 additional patients would be accrued for a total of 26. If at least 14 responses were observed by the end of the second stage the null hypothesis would be rejected, with a 1-sided $\alpha = .0377$ and 80% power.

Data were prospectively collected and stored in a REDCap (Research Electronic Data Capture) database supported by Johns Hopkins. Patient clinicopathological features, treatment history and oncologic outcomes were analyzed. Data were also collected regarding tolerance of treatment and modifications to instillation regimens. Survival probabilities were plotted using the Kaplan-Meier method. Time was calculated from the start of GemDoce induction. RFS was defined by T stage increase from Ta or CIS to T1, development of T2 or greater disease, lymph node positive disease or develop of metastatic disease on axial imaging. Patients were censored at the date of their last cystoscopy if they remained alive and free of HG disease. Adverse events (AEs) were prospectively collected by direct patient interaction classified by the Common Terminology Criteria for Adverse Events v5 (National Cancer Institute, Bethesda, Maryland). Patients were defined as being intolerant to GemDoce if the treatment course was stopped due to symptoms or any serious AE. All statistical testing was 2-sided and

Table 1. *Baseline Characteristics of Study Cohort*

Characteristic	Study cohort (N = 25)
Age, median (IQR), y	68.9 (59.9-73.8)
Male sex, No. (%)	21 (84)
Race, No. (%)	
Caucasian	23 (92)
African American	2 (8)
Smoking status, No. (%)	
Never	10 (40)
Former	13 (52)
Current	2 (8)
Pathologic stage at trial entry, No. (%)	
CIS only	1 (4)
HGTa	7 (28)
HGT1	13 (52)
HGTa with CIS	1 (4)
HGT1 with CIS	3 (12)
Any CIS at trial entry, No. (%)	
Yes	5 (20)
No	20 (80)

Abbreviations: CIS, carcinoma in situ; HG, high-grade; IQR, interquartile range.

assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, North Carolina). The trial received human subjects approval from the Johns Hopkins Institutional Review Board and Cancer Research Committee, and an external Data Safety Monitoring Committee was operated under the auspices of the Sidney Kimmel Comprehensive Cancer Center Compliance Monitoring Program.

RESULTS

Demographics

Twenty-six patients were enrolled into this study from August 2020 to August 2022. One patient at the time of his initial induction dose reported pain from catheterization and instillation, and therefore withdrew from the study and treatments. Twenty-five patients were included in the final analysis of this study (Table 1). The median age was 68.9 (interquartile range 59-73) years. The cohort was predominantly male (21/25 [84%]), Caucasian (23/25 [92%]), and had a history of smoking (15 [60%] any smoking history, 2 [8%] with ongoing tobacco use). Twenty-four patients had papillary disease with or without CIS, including 16 (64%) with HGT1 and 8 (32%) with HGTa. CIS with HGT1 or HGTa was present in 4 (16%) patients. One patient (4%) had CIS only.

Outcomes

The median follow-up time for the cohort was 19.6 months. One hundred percent achieved CR at 3 months and the 12-month RFS was 92% (23/25; 95% CI, 89.9%-94.1%), including 1 patient with a positive cytology with a negative biopsy (Figure 1). No patients with CIS experienced a recurrence at 12-month follow-up. Median time to recurrence was not reached. Both recurrences, 1 at 9 months and 1 at 12 months, had HGT1 recurrences with initial HGT1 path, and are now undergoing intravesical BCG therapy (Figure 2). One patient had a positive urine cytology at the 9-month cystoscopy with negative workup with random biopsies, bilateral upper tract washing, and urine cytology; that patient is continuing on maintenance

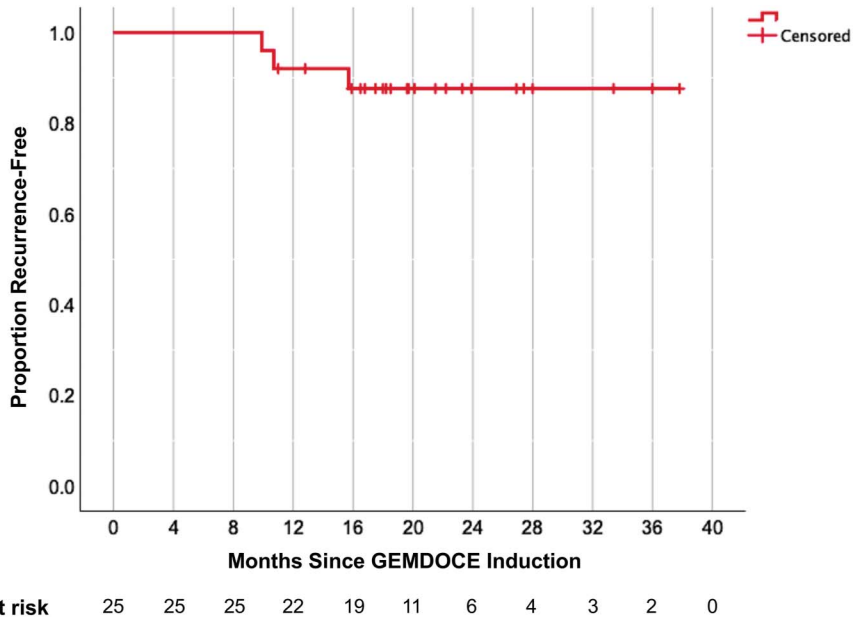

Figure 1. Recurrence-free survival. Kaplan-Meir estimates of recurrence-free survival as a proportion of subjects. The primary endpoint was 3-month complete response, which was defined as the proportion of patients who demonstrated no evidence of recurrent high-grade urothelial carcinoma of the bladder of any stage at the 3-month posttreatment disease assessment; 3-month complete response in this cohort was 100%. The secondary endpoint was 12-month recurrence-free survival, which was 92% (23/25 subjects). GemDoce indicates gemcitabine and docetaxel.

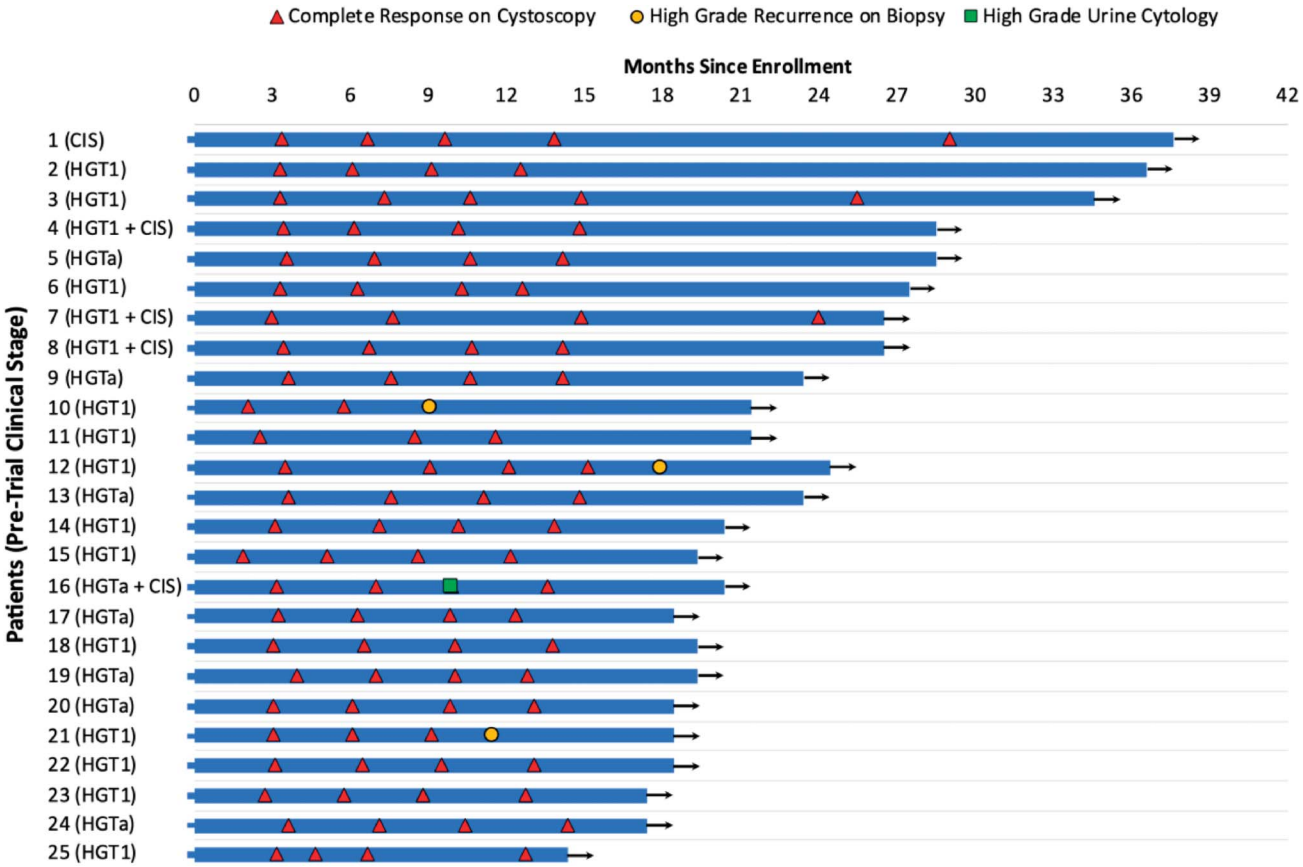

Figure 2. Swimmers plot of individual subjects with their stage, grade, and recurrence status. Two subjects (10 and 21) had pathologically confirmed recurrences within 12 months, and another subject (12) experienced a pathologically confirmed recurrence at 18 months. One subject (16) had a high-grade (HT) urine cytology at 9 months but no cancer was found after random bladder biopsies, prostatic urethral sampling, and bilateral upper tract washes, with subsequent cytologies and cystoscopies showing no cancer. This subject has remained on maintenance treatment. CIS indicates carcinoma in situ.

GemDoce and continues to have no evidence of disease with subsequent negative cytologies. One patient experienced a recurrence at 18 months. No patients progressed to T2 disease, underwent radical cystectomy, and/or harbored radiographic evidence of metastatic or clinically node positive disease.

AEs

Twenty-three patients (92%) reported an AE, with 20 (80%) reporting grade 1, 11 (44%) reporting grade 2, and 5 (20%) reporting grade 3 (Table 2 and Supplemental Table 1, https://www.jurology.com). No grade 4 or 5 AEs were reported (Table 2). Twenty-two patients (82%) did not have any alteration of their schedule due to AE, and 24 patients (96%) completed their induction. One subject required treatment interruption with GemDoce held due to a UTI. Another subject was diagnosed with COVID-19 after first induction leading to treatment delay. Most common AEs were dysuria (24%), fatigue (24%), and respiratory infections (16%, 1 being COVID-19).

DISCUSSION

BCG has been used for NMIBC for more than 50 years, but its dominant position in the treatment of HR NMIBC is beginning to be challenged.[13] The recent shortages of BCG have forced clinicians to seek alternative therapies for NMIBC. Although historic trials have failed to demonstrate non-inferiority of single-agent chemotherapy to BCG, more recent combinatorial strategies have garnered new interest in intravesical chemotherapeutic approaches. To the best of our knowledge, this is the first prospective trial to evaluate the use of GemDoce as a first-line agent in the setting of HR NMIBC. Our study showed durable response with 92% RFS at 12 months. No patient progressed to pT2 disease or required a cystectomy at the time of last follow-up, with 18 (72%) of the cohort having HGT1 or CIS, the highest-risk group for progression and or need for cystectomy. AEs were limited to grade 1 to 3 toxicities, with no patient experiencing grade 4 or 5 events.

In 2015, Steinberg et al published the first known study of sequential GemDoce as an intravesical salvage therapy for patients with NMIBC unresponsive to

Table 2. *Adverse Events Reported in Patients Treated With Sequential Gemcitabine and Docetaxel*

	Patient groups			
	Grade 1	Grade 2	Grade 3	Grade 4 or 5
Total reported adverse events	35	17	7	0
Specific events, No. (%)				
Hematuria	2 (8)	2 (8)	1 (4)	-
UTI	2 (8)	6 (24)	2 (8)	-
Dysuria/suprapubic pain	7 (28)	-	-	
Urinary frequency/urgency	3 (12)	1 (4)	-	-
Nausea/vomiting/gastrointestinal symptoms	3 (12)	2 (8)	-	-
Fatigue	6 (24)	2 (8)	-	-
Gait disturbance	1 (4)	-	-	-
Vasovagal syncope	1 (4)	-	1 (4)	-
Tremor	2 (8)	-	-	-
Headache	1 (4)	-	1 (4)	-
Vision changes/retinopathy	3 (12)	-	-	-
Respiratory infection (including COVID-19)	4 (16)	1 (4)	1 (4)	-
Thrombocytopenia/leukopenia	-	1 (4)	1 (4)	-
Altered mental status	-	1 (4)	-	-
Skin or mucosal rashes or lesions	-	1 (4)	-	-
Patients reporting 1+ adverse event by grade, No. (%)	20 (80)	11 (44)	5 (20)	0 (0)
Patients reporting any adverse event, No. (%)	23 (92)			
Patients not receiving complete induction due to intolerance, No. (%)	1 (4)			
Patients in which side effects affected treatment schedule, No. (%)	3 (12)			

Adverse events are assigned according to Common Terminology Criteria for Adverse Events v5. Percentages of adverse events correspond to number/total instances of reported adverse events.

intravesical therapy, and demonstrated a 54% 1-year and 34% 2-year RFS, in addition to a 66% RFS at first surveillance.[14] We reported similar results with median HG RFS of 56% at 1 year and 42% at 2 years.[15] Since then, GemDoce has been increasingly utilized as a second-line salvage intravesical therapy in patients with BCG-unresponsive NMIBC who choose not to pursue a cystectomy. More recently, GemDoce has been evaluated in a retrospective fashion for BCG-naïve NMIBC, with 12-month RFS reported as 85%.

BCG efficacy is well established, with modern contemporary data showing RFS at 1, 3, and 5 years was 81%, 76%, and 74%, respectively, and progression-free survival was 97%, 93%, and 92% with a median follow-up of 47.8 months.[16] Furthermore, the NIMBUS trial showed similar results with BCG efficacy with 85% RFS at 2 years when standard dosing was used.[17] However, BCG is notoriously challenging to manufacture, and worldwide shortages are commonplace. Recent years have witnessed enhanced innovation and drug development for BCG-unresponsive NMIBC, as efforts increased to find alternatives to BCG particularly in times of shortage. In 2020 the FDA (Food and Drug Administration) approved pembrolizumab and in 2022 it approved nadofaragene firadenovec-vncg for the treatment of BCG-unresponsive CIS. These 2 approvals comprised the first in more than 20 years in the NMIBC space, and still more approvals are likely to come in the coming years. Despite both pembrolizumab and now nadofaragene firadenovec being FDA approved for this indication, GemDoce continues to be a mainstay treatment for NMIBC. How these drugs will be utilized will ultimately depend on their efficacy relative to their toxicity. In our cohort, dysuria (24%) and fatigue (24%) constituted the most common AEs with GemDoce, and while these data appear to be comparable with published AE profile of BCG, ultimately head-to-head trials are necessary for direct comparisons that will impact physician and patient decision-making.

While this is the first prospective clinical trial to evaluate GemDoce, it is not without limitations. This study is from a high-volume single center and incorporated a single arm without a comparator. The presence of CIS continues to be an independent driver of unresponsiveness to BCG.[16] Our study comprised 20% of patients with CIS, none of whom experienced a recurrence within 1 year. Nevertheless, this relatively low contribution of CIS patients may mean that some of our patients may have been cured with TURBT alone for their papillary disease, and the treatment effect of GemDoce is thus overstated. There are elements of single-arm designs that have limitations; however, this is the first prospective trial evaluating intravesical GemDoce for NMIBC, and BCG-naïve NMIBC in particular. As such, this is the first prospective report of safety and toxicity as well as baseline efficacy on protocol. The trial was single arm as the study was designed during and carried out through a severe BCG shortage, with the intent to have a follow-on phase 3 randomized trial to directly compare GemDoce to BCG. These prospective data suggest 12-month efficacy consistent with (1) prior retrospective GemDoce efficacy data and (2) prior BCG efficacy data, and this provides rationale for direct head-to-head comparison of BCG and GemDoce. Ecog-Acrin 8212 "BRIDGE" is a phase 3, randomized, controlled trial comparing BCG to GemDoce that is

currently open to accrual. This trial, with a planned enrollment of 870 patients, will be stratified by papillary and CIS histologies and will be able to address some of the limitations of both retrospective series and single-arm prospective trials.

CONCLUSIONS

In this first prospective phase 2 clinical trial to evaluate intravesical GemDoce for BCG-naïve NMIBC, 100% of patients had 3-month CR and 92% had 12-month RFS. Grade 3 AEs were found to be 20%. A randomized trial directly comparing GemDoce to BCG for newly diagnosed HR-NMIBC is currently underway.

ACKNOWLEDGMENTS

We dedicate this study to the memory of Alan Partin, MD, PhD, who allocated a gift from the Chad Holliday Research Fund to support this trial. We also thank Aliya Lalji, Azeem Bhatti, and Ting Wang for their oversight of the study's regulatory and personnel needs.

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EDITORIAL COMMENTS

This trial presents valuable insights into intravesical gemcitabine and docetaxel (GemDoce) as an alternative to bacillus Calmette-Guérin (BCG) in the first-line treatment of patients with high-risk nonmuscle-invasive bladder cancer (HR NMIBC).[1] The cohort consisted of 25 patients with typical high-risk characteristics including 64% T1 and 20% carcinoma in situ–containing disease. Corroborating prior retrospective reports,[2] the 3-month complete response rate was 100% and 12-month recurrence-free survival was 92%. No patients progressed to pT2 disease or required cystectomy. Importantly, GemDoce was safe, with an absence of grade 4 or 5 adverse events and

predominantly grade 1 and 2 adverse events such as dysuria and fatigue.

Several strategies have been evaluated for the first-line treatment of HR NMIBC, with randomized data supporting BCG over single-agent chemotherapy. Efficacy and tolerability have traditionally been significant concerns, but the issue of BCG shortage has emerged as a more contemporary problem.[3] Novel strategies include combination therapies with BCG (checkpoint inhibition, IL-15 superagonist) to improve efficacy. However, the ideal approach given the BCG shortage is to find a regimen that does not rely on BCG.

GemDoce is one such option that utilizes standard intravesical administration schedules that most urologists are familiar with. While the data presented here and in larger retrospective series suggest similar efficacy to BCG, it is important to acknowledge the potential for lower costs with GemDoce, an important consideration for both patients and our health care systems.[4]

Ultimately, we need prospective validation prior to widespread adoption and implementation of GemDoce as the first-line treatment for patients with HR NMIBC. This phase 2 study confirms robust response rates and an acceptable safety profile. The ongoing phase 3 BRIDGE trial (NCT05538663) will clarify the future role of BCG and GemDoce in this space, while also facilitating investigation of predictors of response to either treatment.

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The authors present their single-arm phase 2 trial of 25 patients with bacillus Calmette-Guérin (BCG)–naïve high-risk nonmuscle-invasive bladder cancer (HR NMIBC) treated with induction plus maintenance intravesical gemcitabine and docetaxel (GemDoce).[1] This cohort represents an especially high-risk population as almost three-fourths had HGT1 or carcinoma in situ. Notably, 100% of patients achieved a complete response at 3 months and 92% remained disease-free at 12 months, surpassing contemporary BCG recurrence-free survival (RFS) rates of roughly 80% at 1 year.[2] While most patients experienced at least a low-grade treatment-related toxicity, only one person could not complete the induction course.

GemDoce has quickly become a popular alternative to BCG in areas of shortage and second-line intravesical option in cases of BCG unresponsiveness. Further insight into the efficacy and toxicity is forthcoming with the actively-enrolling "BRIDGE" trial. This phase 3 prospective randomized controlled trial of BCG versus GemDoce as primary therapy for HR NMIBC will clarify whether upfront GemDoce RFS rates land closer to the excellent response found in this study or drift toward the 54% 1-year RFS reported by Steinberg et al[3] in the BCG-unresponsive stage. Beyond comparing disease outcomes, translational endpoints may indicate whether the antitumor activity of GemDoce is additive or synergistic and elucidate biomarkers to guide treatment strategies. Jong et al recently described three molecular subtypes of HR NMIBC characterizing innate BCG-responsiveness.[4] A comprehensive phenotypic system such as this will be paramount to help providers navigate our ever-expanding catalog of therapeutic options and route patients toward the most efficacious first-line treatment option.

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REPLY BY AUTHORS

We greatly appreciate the editorial comments regarding our publication in the *Journal of Urology*®.[1] Although transurethral resection of bladder tumor plus adjuvant intravesical bacillus Calmette-Guérin (BCG) remains the gold-standard treatment for patients with intermediate- and high-risk nonmuscle-invasive bladder cancer, there are both logistical and oncologic concerns with relying exclusively on this treatment paradigm. There have been 3 major BCG shortages in the last decade, 5% to 10% of patients cannot tolerate BCG due to side effects, and 30% to 50% of patients will have recurrent disease within 2 years despite adequate BCG therapy.[2] These shortcomings underscore the need for alternative first-line and salvage therapy options that allow for bladder preservation.[3]

As the editorial comments astutely point out, despite the encouraging prospective data presented in our single-center single-arm phase 2 study, there are many unanswered questions regarding the efficacy, durability, and tolerability of intravesical gemcitabine and docetaxel (GemDoce) as a first-line agent in patients with high-risk nonmuscle-invasive bladder cancer. It is unclear whether the high recurrence-free survival and lack of high-grade toxicities observed in our cohort will be replicated by phase 3 trials randomizing patients to BCG or GemDoce in an analogous patient population, particularly if a higher proportion of patients with carcinoma in situ are included. The actively enrolling phase 3 multicenter noninferiority BRIDGE trial will provide important data regarding key oncologic endpoints (eg, high recurrence-free survival, cystectomy-free survival, overall survival), safety endpoints (eg, toxicity, patient-reported quality-of-life outcomes), and correlative biomarker data to identify which patients benefit most from GemDoce in a prospective manner.[4]

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